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N-Methyl-N-phenyl-5-oxa-1-azaspiro[2.5]oct-1-en-2-amine — Synthesis and Reactions of a Synthon for an Unknown -Amino Acid

Löpfe, M ; Heimgartner, H ; Linden, Anthony

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***N*-METHYL-*N*-PHENYL-5-OXA-1-AZASPIRO[2.5]OCT-1-EN-2-AMINE –
SYNTHESIS AND REACTIONS OF A SYNTHON FOR AN UNKNOWN
 α -AMINO ACID**

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Dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday

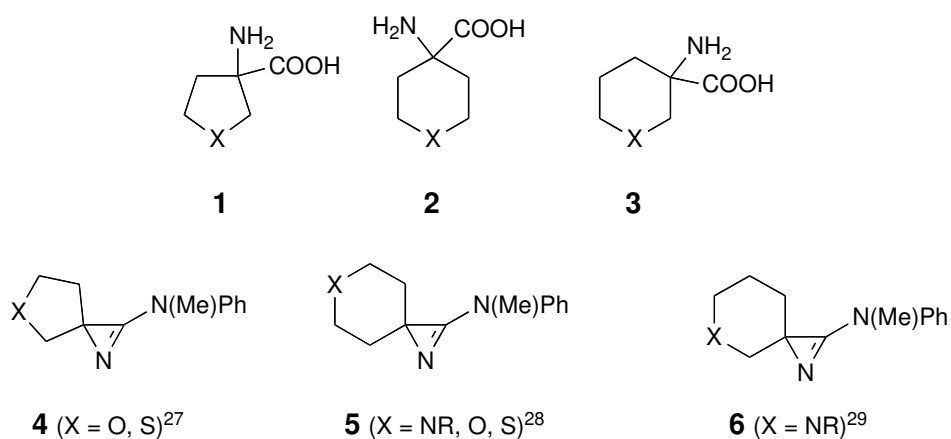
Abstract – The synthesis of the heterospirocyclic amino azirine *N*-methyl-*N*-phenyl-5-oxa-1-azaspiro[2.5]oct-1-en-2-amine (**6a**) was achieved from 3,4-dihydro-2*H*-pyrane (**7**) via *N*-methyl-*N*-phenyltetrahydropyran-3-thiocarboxamide (**11**). The reactions of **6a** with thiobenzoic acid and Z-Phe-OH, respectively, leading to the corresponding 3-benzoylamino-tetrahydropyran-3-thiocarboxamide (**13**) and the diastereoisomeric dipeptide amides (**14**), respectively, demonstrate that **6a** is a valuable synthon for the hitherto unknown 3-aminotetrahydropyran-3-carboxylic acid. The structure of **13** was established X-Ray crystallography.

INTRODUCTION

Knowledge of the conformation of peptides and proteins is of central importance for the understanding of their biological functions. Therefore, there is continuing interest in the factors which determine the local or global conformation as the basis for peptide design. Among a series of structural modifications of natural α -amino acids, the α -alkylation is known to restrict the conformational freedom significantly.²⁻⁵ The most well-known α,α -disubstituted α -amino acid is 2-aminoisobutyric acid (Aib), which is widespread in nature, e.g., in linear, amphiphilic polypeptides called ‘peptaibols’.^{6,7} Aib and many other α,α -disubstituted α -amino acids enhance the tendency of peptides to adopt defined secondary structures like β -turns or helices. This structural quality is a prerequisite for these peptides to form ion channels

through membranes⁸ and to act as antibiotics.⁹ Recently, their activity as cytotoxic substances has also been studied.¹⁰

A special group of α,α -disubstituted α -amino acids are 1-aminocycloalkane-1-carboxylic acids. It was demonstrated that they also show biological activities,^{11,12} and their influence on peptide conformations is similar to that of Aib.^{13,14} Furthermore, heterocyclic α -amino acids of type **1**,^{15–17} **2**,^{16b,18–20} and **3**^{18c,19a,21} (X = NR, O, S) were studied with the same goal. Whereas in the cases of **1** and **2** the N, O, and S-analogues were used, only the N and S derivatives of type **3** were included. Surprisingly, the analogous 3-aminotetrahydropyran-3-carboxylic acid (**3**, X = O) is hitherto unknown.

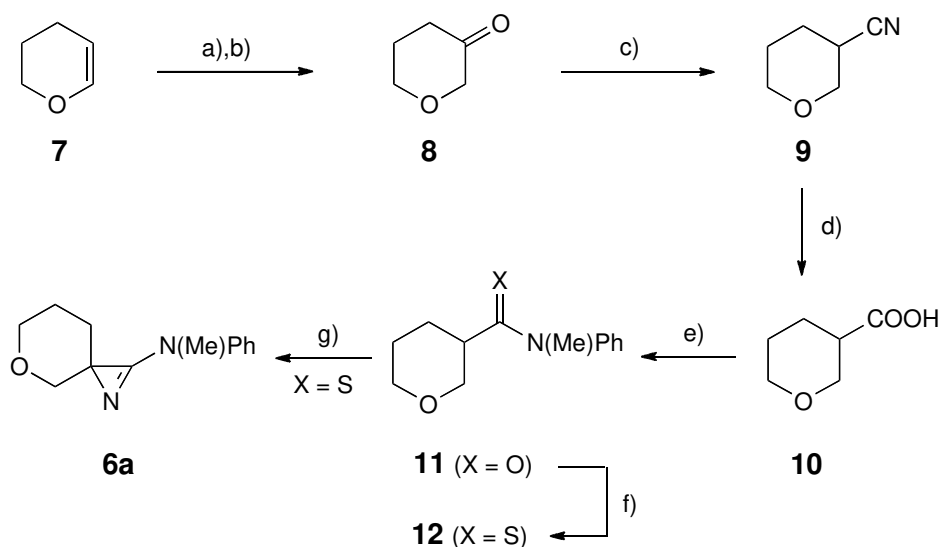


In the past, we have shown that 2,2-disubstituted 2*H*-azirine-3-amines are useful building blocks for α,α -disubstituted α -amino acids.^{22,23} The so-called ‘azirine/oxazolone method’ was successfully used to synthesize linear and cyclic peptides and depsipeptides, which contain α,α -disubstituted α -amino acids in their backbone.^{24–26} For this reason, we have prepared a series of 2,2-disubstituted 2*H*-azirine-3-amines, including heterospirocyclic ones. For example, the azirines (**4** – **6**) were used as synthons for the corresponding amino acids (**1** – **3**). The chiral building blocks **4** and **6** were synthesized as racemates. Because the heterocyclic amino acid (**3**, X = O) was not known, we decided to prepare the related synthon **6a** (= **6**, X = O) and to evaluate if it can be used in peptide synthesis.

RESULTS AND DISCUSSION

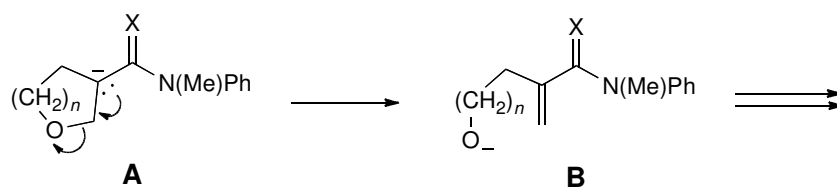
We planned the synthesis of **6a** in analogy to earlier described approaches, i.e., the transformation of *N*-methyl-*N*-phenyltetrahydrofuran-3-carboxamide into the azirine under the conditions described in ref.²⁹ Therefore, the corresponding tetrahydrofuran-3-carboxylic acid (**10**) had to be prepared first. Although the synthesis of this acid via acid-catalyzed dimerization of acrolein, followed by oxidation of the aldehyde group and hydrogenation of the C=C bond was described repeatedly (e.g. ref.³⁰), we decided to carry out the synthesis as depicted in *Scheme 1*.

Scheme 1



Reagents and conditions: a) 1. $\text{BH}_3 \cdot \text{THF}$, THF, 0 °C; 2. NaOH, H_2O_2 , 25 °C; b) PCC, molecular sieves (3Å), CH_2Cl_2 , rt; c) Tosmic, *t*-BuOK, *t*-BuOH/DME, 0 °C → rt; d) NaOH, EtOH/ H_2O , reflux; e) 1. SOCl_2 , reflux; 2. Ph(Me)NH , Et_3N , CH_2Cl_2 , 0 °C → rt; f) Lawesson reagent, toluene, 110 °C; g) 1. COCl_2 in toluene, CH_2Cl_2 , DMF, 0 °C; 2. DABCO, THF, rt; 3. NaN_3 , DMF/THF, rt

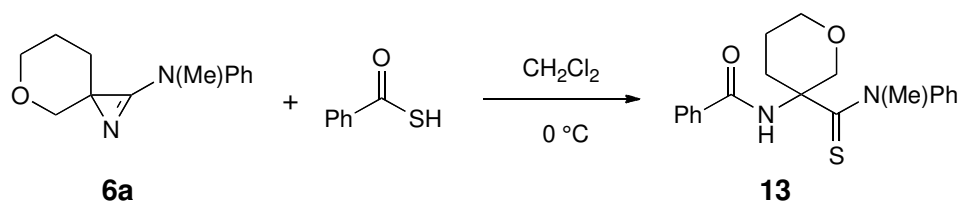
The hydroboration of 3,4-dihydro-2H-pyran (**7**) with the $\text{BH}_3 \cdot \text{THF}$ complex was performed according to the protocol of Brown et al.,³¹ which gave 3-hydroxytetrahydropyran in the modest yield of 47%. Subsequent oxidation was performed under various conditions, and the best result (90% yield of **8**) was obtained by using pyridinium chlorochromate (PCC) in the presence of molecular sieves (3Å) at room temperature.³² As in a previously described example,²⁸ the transformation of **8** into the nitrile **9** was achieved according to the method of Oldenzien and van Leusen,³³ that is by treatment with tosylmethyl isocyanate (Tosmic) and potassium *tert*-butanolate at room temperature (48% yield). Finally, saponification with NaOH in ethanol/water (1:2) under reflux led to the desired acid **10** in 95% yield. A solution of the acid (**10**) in thionyl chloride was heated to reflux to give the acid chloride in quantitative yield, which was reacted with *N*-methylaniline under standard conditions. After chromatographic purification, *N*-methyl-*N*-phenyltetrahydropyran-3-carboxamide (**11**) was obtained in 90% yield. Surprisingly, all attempts to convert **11** into the desired azirine (**6a**) according to the method described in ref.²⁹ and successfully applied for the synthesis of azirines of type (**5**)²⁸ failed, and, in addition to starting amide (**11**), a mixture of unidentified products was detected (NMR). A similar result was obtained in the attempted synthesis of **4** (X = O).^{27a} A possible explanation is the ring opening **A** → **B** under strong basic conditions, leading to acrylamide derivatives, which undergo further reactions.



Finally, we succeeded in the preparation of azirine (**6a**) via a modification³⁴ of the classical method of Rens and Ghosez.³⁵ The amide (**11**) was transformed into the corresponding thioamide (**12**) by treatment with Lawesson reagent in boiling toluene (ref.²⁷), which was then reacted sequentially with phosgene in dichloromethane and catalytic amounts of dimethylformamide (DMF), 1,4-diazabicyclo[2.2.2]octane (DABCO) in THF, and sodium azide in DMF/THF (*Scheme 1*). After chromatographic purification, **6a** was obtained in 82% yield, contaminated with small amounts of the amide (**11**).³⁶ The IR spectrum of **6a** showed the characteristic C=N absorption at 1756 cm^{-1} and the base-peak in the CI-MS appeared at m/z 217 ($[M+1]^+$). All other spectroscopic data were in accordance with the structure.

A chemical proof for the ‘aminoazirine structure’ is the reaction with thiobenzoic acid.^{27–29} For this reason, 1.15 mol-equivalents of thiobenzoic acid were added to a solution of **6a** in dichloromethane at $0\text{ }^{\circ}\text{C}$. After only 10 min, the reaction was almost complete. Chromatographic workup gave the expected thioamide (**13**) in 93% yield (*Scheme 2*). The structure of the product was elucidated on the basis of the spectroscopic data and elemental analysis. Indicative were the ESI-MS with m/z 377 for $[M+\text{Na}]^+$ and the ^{13}C -NMR spectrum with a signal at 203.5 ppm for the thioamide C-atom. Finally, single crystals were obtained from ethyl acetate/hexane, and the crystal-structure was established by X-Ray crystallography (*Figure 1*).

Scheme 2



Since the space group of **13** is centrosymmetric, the crystals are racemic. The torsion angles $\phi(\text{C}(1)\text{--N}(2)\text{--C}(3)\text{--C}(4))$ and $\psi(\text{N}(2)\text{--C}(3)\text{--C}(4)\text{--N}(5))$ of the tetrahydropyran-3-yl residue are $59.8(2)$ and $37.5(2)^{\circ}$, respectively. These values are very close to those expected for an amino acid involved in a β -turn of type *I* or *III*³⁸. Very similar torsion angles have been observed for heterocyclic amino acids **1** ($\text{X} = \text{O}$) and **2** in short peptides and thiopeptides.^{27a,28,39} The six-membered heterocycle adopts a chair conformation. Surprisingly, the amide group does not partake in any hydrogen bonding interactions.

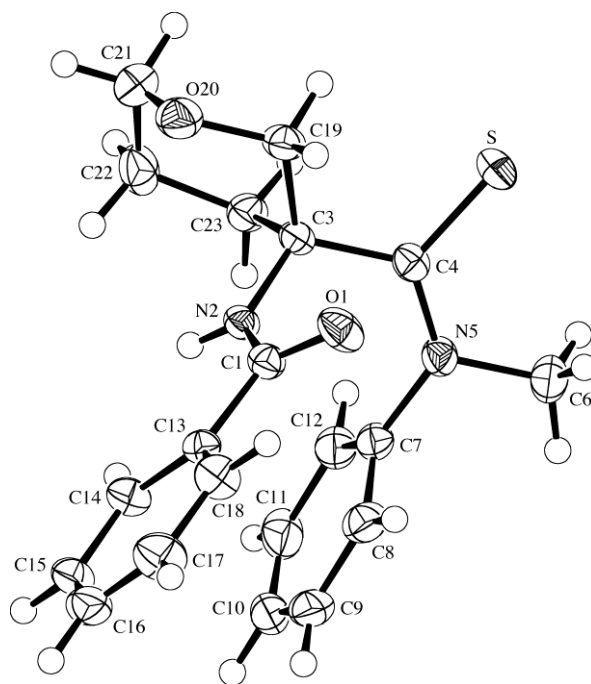


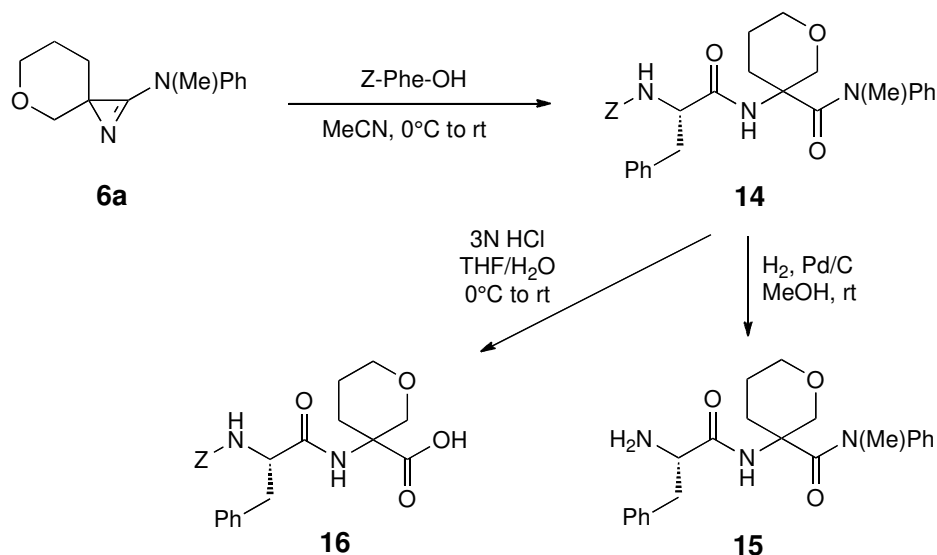
Figure 1. ORTEP plot³⁷ of the molecular structure of **13** (arbitrary numbering of the atoms; 50% probability ellipsoids)

With the aim of testing the potential of **6a** as an amino acid synthon in the synthesis of peptides, the reaction with Z-Phe-OH was performed in acetonitrile. After addition of 1.1 mol-equivalents of Z-Phe-OH at 0 °C and stirring the mixture for 60 h at room temperature, the protected dipeptide amide (**14**) was obtained in quantitative yield as a mixture of two diastereoisomers (*Scheme 3*). The 1:1 ratio of the diastereoisomers was determined by means of ¹H- and ¹³C-NMR spectroscopy as well as by chromatography (HPLC, Nucleosil 100-7). Again, the structure of **14**, as a mixture of diastereoisomers, was determined on the basis of the spectroscopic data, the ESI-MS with *m/z* 538 ([*M*+Na]⁺, 100%), and elemental analysis. In a small-scale HPLC experiment, the separation of the diastereoisomers of **14** was achieved.

An additional prerequisite for the use of **6a** in peptide synthesis is the selective deprotection of the N- and C-termini of the coupling products. For the model dipeptide (**14**), this means that the transformation to the free amino component (**15**) as well as that to the peptide acid (**16**) should be possible selectively. The deprotection of the amino group of **14** via hydrogenolysis was carried out under standard conditions with Pd on charcoal in methanol at room temperature to give **15** as a 1:1 mixture of diastereoisomers (HPLC). The separation of the isomers was accomplished by column chromatography on silica gel; the two isomers were obtained in 27 and 28% yield, respectively. The selective hydrolysis of the terminal amide group of **14** was achieved under mild conditions by treatment with 3N HCl in H₂O/THF at room temperature. After 4 h, chromatographic workup gave 58% of **16** as a 1:1 mixture of diastereoisomers and

ca. 25% of the starting material **14**. All attempts to separate the diastereoisomeric dipeptide acids of type (**16**) by column chromatography were unsuccessful.

Scheme 3



CONCLUSIONS

A practical synthesis of the heterospirocyclic 2*H*-azirin-3-amine (**6a**) was elaborated. The coupling reactions of **6a** with thiobenzoic acid and *Z*-protected phenylalanine, respectively, together with the subsequent selective deprotection of the amino and carboxyl group of the coupling product, i.e., the protected dipeptide (**14**), demonstrated that **6a** is a useful synthon for the hitherto unknown 3-aminotetrahydropyran-3-carboxylic acid (**3**, X = O).

EXPERIMENTAL

General remarks. TLC: silica gel 60 F₂₅₄ plates (0.25 mm, Merck). Column chromatography (CC): silica gel 60 (0.043–0.063 mm, Merck). High performance liquid chromatography (HPLC): Nucleosil 100-7 (Machery-Nagel); UV-detection (λ = 240 nm; Varian 2550 or Jasco UV-975). Melting points: Büchi B-540 apparatus, uncorrected. IR spectra: Perkin-Elmer-Spektrum ONE FT-IR, in KBr or as film; in cm⁻¹. ¹H-NMR (300 MHz) and ¹³C-NMR (75 MHz) spectra: Bruker AC-300 and ARX-300 instrument, in CDCl₃; chemical shifts in ppm, coupling constants *J* in Hz. The multiplicities of ¹³C signals were determined with DEPT 135 and DEPT 90 measurements, and the assignments of ¹H signals were made on the basis of COSY experiments. EI-MS (70 eV) and CI-MS (NH₃ as carrier gas): Finnigan MAT-95 or Finnigan SSQ-700 instrument. ESI-MS: Finnigan TSQ-700. Elemental analyses were carried out on a Vario-EL (Elementar) instrument.

Synthesis of *N*-methyl-*N*-phenyl-5-oxa-1-azaspiro[2.5]oct-1-en-2-amine (6a). *Tetrahydropyran-3-ol*.³¹

To a solution of 3,4-dihydro-2*H*-pyran (**7**) (17.5 mL, 16.24 g, 193 mmol) in THF (82 mL) at 0 °C was added drop-wise BH₃·THF (95 mL of a 1M solution in THF, 8.29 g, 95 mmol) and the mixture stirred for 3 h at 0 °C. Then, 3N NaOH (64 mL) and a 30% H₂O₂-solution (31 mL) were added drop-wise at 0 °C, and the mixture was stirred for 5 h at rt. After addition of K₂CO₃ (100 g), the organic phase was separated, the aqueous phase extracted with Et₂O (3 × 150 mL), and the combined organic phase was dried with MgSO₄. The solvent was evaporated, and the residue distilled at 65 °C (3 mbar) yielding 9.30 g (47%) of tetrahydropyran-3-ol as colorless oil. IR (film): 3406vs, 2942vs, 2854vs, 2753w, 1469s, 1441vs, 1381s, 1366s, 1297s, 1254s, 1208s, 1174s, 1144s, 1084vs, 1029vs, 995vs, 979s, 963vs, 913vs, 871vs, 845m, 803m, 712m. ¹H-NMR: 3.79–3.51 (*m*, CH₂(2), CH₂(6)); 3.42–3.36 (*m*, CH(3)); 2.44 (br. *s*, OH); 1.96–1.77, 1.65–1.48 (2*m*, CH₂(4), CH₂(5)). ¹³C-NMR: 72.9 (*t*, C(2)); 68.0 (*t*, C(6)); 65.8 (*d*, C(3)); 31.4, 23.1 (2*t*, C(4), C(5)). EI-MS: 102 (49, *M*⁺), 84 (17, [*M*-H₂O]⁺), 74 (10, [C₄H₆O]⁺), 72 (24), 71 (45, [*M*-CH₂OH]⁺), 70 (36, [*M*-CH₃OH]⁺), 59 (6), 58 (21), 57 (34, [C₃H₅O]⁺), 56 (15), 55 (14), 45 (43), 44 (100, [C₂H₄O]⁺).

Tetrahydropyran-3-one (**8**).⁴⁰ According to the protocol in ref.³², pyridinium chlorochromate (PCC) (94.98 g, 440 mmol) and ground molecular sieves 3 Å (88.12 g) were suspended in CH₂Cl₂ (300 mL), and a solution of tetrahydropyran-3-ol (18.00 g, 176 mmol) in CH₂Cl₂ (140 mL) was added. After stirring for 2.5 h at rt, Et₂O (400 mL) was added and the suspension filtered through silica gel (containing 7% MgSO₄). Purification by CC (pentane/Et₂O 1:4) gave 15.82 g (90%) **8** as colorless oil. IR (film): 2961s, 2859m, 1724vs, 1446w, 1417m, 1337w, 1317m, 1289w, 1247s, 1194s, 1166m, 1102vs, 1036w, 985w, 940w, 915s, 857m, 734w, 647w. ¹H-NMR: 4.01 (*s*, CH₂(2)); 3.95–3.75 (*m*, CH₂(6)); 2.53 (*t*, *J* = 6.9, CH₂(4)); 2.19–2.00 (*m*, CH₂(5)). ¹³C-NMR: 207.4 (*s*, CO); 74.8 (*t*, C(2)); 65.8 (*t*, C(6)); 37.3 (*t*, C(4)); 24.7 (*t*, C(5)). EI-MS: 100 (57, *M*⁺), 71 (24), 70 (14), 55 (9, [C₃H₃O]⁺), 45 (10), 44 (6), 43 (12), 42 (100, [C₂H₂O]⁺).

Tetrahydropyran-3-carbonitrile (**9**).⁴¹ According to ref.³³, a solution of *t*-BuOK (11.26 g, 100 mmol) in *t*-BuOH/dimethoxyethane (DME) 1:1 (200 mL) was added to a solution of **8** (5.00 g, 49.94 mmol) and tosylmethyl isocyanide (Tosmic) (10.73 g, 54.98 mmol) in DME (200 mL) at 0 °C. After stirring the mixture for 1.5 h at 0 °C and 2 h at rt, Et₂O (100 mL) was added. The mixture was washed with an aqueous 5%-solution of NaHCO₃ (2×), dried over NaSO₄, and the solvent evaporated. Distillation at 70 °C, 0.15mbar (Kugelrohr) yielded 2.672 g (48%) of **9** as colorless oil. IR (film): 2954vs, 2857vs, 2241s, 1470s, 1453s, 1438s, 1386w, 1363w, 1326w, 1301w, 1276m, 1249w, 1217m, 1197vs, 1177s, 1148w, 1098vs, 1083s, 1068vs, 1034s, 1015s, 967m, 947w, 910s, 878vs, 863s, 832m, 786w, 687w.

¹H-NMR: 3.87 (*dd*, *J* = 11.4, 3.3, 1 H of CH₂(2)); 3.74–3.61 (*m*, 1 H of CH₂(2), 2 H of CH₂(6)); 2.80–2.72 (*m*, CH(3)); 2.10–2.00 (*m*, 1 H of CH₂(4)); 1.96–1.76 (*m*, 1 H of CH₂(4), 1 H of CH₂(5)); 1.67–1.54 (*m*, 1 H of CH₂(5)). ¹³C-NMR: 119.9 (*s*, CN); 68.2, 67.9 (*2t*, C(2), C(6)); 27.6 (*d*, C(3)); 26.5, 23.4 (*2t*, C(5), C(4)).

Tetrahydropyran-3-carboxylic acid (**10**).³⁰ To a solution of NaOH (11.77 g, 294 mmol) in H₂O (100 mL) and EtOH (50 mL) was added **9** (3.254 g, 29.31 mmol), dissolved in a small amount of EtOH, and the mixture was stirred for 2.5 h under reflux. After cooling to 0 °C, conc. HCl (33.5 mL) was added and EtOH evaporated. The residue was extracted with CH₂Cl₂ (3×) and dried over MgSO₄. Recrystallization from CH₂Cl₂ yielded 3.61 g (95%) of **10** as colorless crystals. IR (KBr): 2952*vs*, 2859*s*, 1706*vs*, 1469*m*, 1453*m*, 1438*m*, 1418*m*, 1282*s*, 1196*vs*, 1145*m*, 1105*s*, 1082*s*, 1035*m*, 1014*m*, 968*m*, 913*s*, 861*s*, 834*m*, 813*m*, 733*m*, 648*w*. ¹H-NMR: 4.01 (*ddd*, *J* = 11.4, 4.0, 1.2, 1 H of CH₂(2)); 3.85–3.80 (*m*, 1 H of CH₂(6)); 3.64 (*dd*, *J* = 11.4, 8.7, 1 H of CH₂(2)); 3.53–3.45 (*m*, 1 H of CH₂(6)); 2.68–2.59 (*m*, CH(3)); 2.08–2.00 (*m*, 1 H of CH₂(4)); 1.86–1.59 (*m*, 1 H of CH₂(4), 2 H of CH₂(5)). ¹³C-NMR: 178.3 (*s*, CO); 68.5, 68.0 (*2t*, C(2), C(6)); 41.1 (*d*, C(3)); 25.5, 24.4 (*2t*, C(5), C(4)).

N-Methyl-N-phenyltetrahydropyran-3-carboxamide (**11**). Thionylchloride (1.2 mL, 1.95 g, 16.41 mmol) was added slowly to **10** (0.30 g, 2.305 mmol) and the mixture heated to reflux. After 2 h, the evolution of SO₂ ceased, and after an additional 1 h, the mixture was cooled to rt, the excess of SOCl₂ was evaporated under high vacuum, and the residue dried under high vacuum yielding 0.34 g (99%) tetrahydropyran-3-carboxylic acid chloride as a brownish oil. This acid chloride (0.34 g, 2.288 mmol) was dissolved in CH₂Cl₂, and *N*-methylaniline (0.30 mL, 2.739 mmol) and triethylamine (0.35 mL, 2.534 mmol) were added drop-wise. The mixture was stirred for 4 h at rt, the solvent evaporated, the residue dissolved in ethyl acetate (AcOEt) and filtered. After CC (30 g SiO₂, hexane/AcOEt 2:1) and drying under high vacuum, 0.451 g (90%) of **11** were obtained as colorless solid; mp 96–97 °C. IR (KBr): 3059*w*, 2980*m*, 2953*s*, 2926*s*, 2848*s*, 1645*vs*, 1593*s*, 1495*s*, 1456*s*, 1421*vs*, 1383*vs*, 1362*s*, 1344*m*, 1328*m*, 1310*s*, 1289*s*, 1254*m*, 1215*s*, 1176*m*, 1103*vs*, 1083*vs*, 1035*s*, 1024*m*, 995*s*, 969*m*, 938*w*, 912*s*, 876*m*, 860*m*, 790*w*, 777*s*, 729*w*, 701*vs*, 670*s*. ¹H-NMR: 7.46–7.33 (*m*, 3 arom. H); 7.20–7.16 (*m*, 2 arom. H); 3.87–3.76 (*m*, 1 H of CH₂(2), 1 H of CH₂(6)); 3.51 (*t*, *J* = 10.9, 1 H of CH₂(2)); 3.33 (*dt*, *J* = 11.9, 2.5, 1 H of CH₂(6)); 3.22 (*s*, MeN); 2.60–2.53 (*m*, CH(3)); 1.86–1.78 (*m*, CH₂(4)); 1.53–1.35 (*m*, CH₂(5)). ¹³C-NMR: 172.8 (*s*, CO); 143.6 (*s*, 1 arom. C); 129.7, 127.8, 126.9 (*3d*, 5 arom. CH); 69.5, 67.7 (*2t*, C(2), C(6)); 40.2 (*d*, C(3)); 37.1 (*q*, MeN); 26.5, 24.7 (*2t*, C(5), C(4)). CI-MS (NH₃): 221 (14), 220 (100, [M+H]⁺), 107 (5, [M–C₆H₉O₂+H]⁺). Anal. Calcd for C₁₃H₁₇NO₂: C, 71.21; H, 7.81; N, 6.39: Found: C, 71.18; H, 7.36; N, 6.29.

N-Methyl-N-phenyltetrahydropyran-3-thiocarboxamide (**12**). A suspension of **11** (0.509 g, 2.321 mmol) and Lawesson-Reagents (1.136 g, 2.809 mmol) in toluene (9 mL) was heated to 110 °C for 2.5 h. After cooling to rt, the mixture was filtered through *Celite*. The residue was purified by CC (SiO₂, hexane/AcOEt 1:2), the solvent evaporated, and the residue dried under high vacuum overnight. After additional CC (SiO₂, CH₂Cl₂), 0.396 g (74%) of **12** were obtained as colorless solid; mp 103–104 °C. IR (KBr): 2971*m*, 2943*s*, 2923*s*, 2854*s*, 1591*m*, 1492*vs*, 1451*vs*, 1381*vs*, 1362*s*, 1342*m*, 1323*m*, 1302*m*, 1274*s*, 1220*s*, 1184*s*, 1172*s*, 1099*vs*, 1077*vs*, 1028*vs*, 999*m*, 984*m*, 959*w*, 911*vs*, 884*m*, 861*m*, 837*s*, 796*m*, 777*s*, 734*s*, 701*vs*, 624*m*. ¹H-NMR: 7.52–7.40 (*m*, 3 arom. H); 7.16 (*d*, *J* = 6.8, 2 arom. H); 3.83–3.72 (*m*, CH₂(2), 1 H of CH₂(6)); 3.68 (*s*, MeN); 3.36 (*dt*, *J* = 12.1, 2.4, 1 H of CH₂(6)); 2.90–2.80 (*m*, CH(3)); 2.09 (*m*, 1 H of CH₂(4)); 1.82–1.77 (*m*, 1 H of CH₂(4)); 1.52 (*dd*, *J* = 13.5, 1.9, 1 H of CH₂(5)); 1.43–1.33 (*m*, 1 H of CH₂(5)). ¹³C-NMR: 205.8 (*s*, CS); 145.3 (*s*, 1 arom. C); 130.1, 128.6, 125.3 (3*d*, 5 arom. CH); 72.6, 67.7 (2*t*, C(2), C(6)); 47.6 (*d*, C(3)); 45.2 (*q*, MeN); 30.7, 25.0 (2*t*, C(5), C(4)). CI-MS (NH₃): 238 (5), 237 (15), 236 (100, [M+H]⁺). Anal. Calcd for C₁₃H₁₇NOS: C, 66.35; H, 7.28; N, 5.95; S, 13.62. Found: C, 66.34; H, 6.70; N, 5.89; S, 13.64.

N-Methyl-N-phenyl-5-oxa-1-azaspiro[2.5]oct-1-en-2-amine (**6a**). To a stirred solution of **12** (0.858 g, 3.645 mmol) in CH₂Cl₂ (4.9 mL) containing 3 drops of DMF at 0 °C, a 2M solution of phosgene (2.35 mL, 4.700 mmol) in toluene was added (CO₂ evolution). After stirring for 1 h at rt, the solvent was evaporated, the residue was dissolved in THF (10 mL), and 1,4-diazabicyclo[2.2.2]octane (DABCO) (530 mg, 4.713 mmol) was added. After stirring for 40 min at rt, the brownish precipitate was filtered off under an N₂ atmosphere and washed twice with DMF (10 mL). To the filtrate was added NaN₃ (766 mg, 11.786 mmol), and the mixture was stirred for 4 d at rt under N₂. Then, Et₂O was added to the mixture, which was filtered through *Celite*. After CC (SiO₂, hexane/CH₂Cl₂/AcOEt = 1:0.5:2), a mixture of **11** (7%) and **6a** was obtained as a yellow, viscous oil (¹H-NMR): 649 mg (corresponds to 604 mg of **6a**, 82% yield). IR (film): 2941*m*, 2841*m*, 1756*vs* (ν_{C=N}), 1600*s*, 1502*s*, 1459*w*, 1422*w*, 1355*w*, 1320*m*, 1285*w*, 1257*w*, 1237*w*, 1113*w*, 1086*s*, 1028*w*, 949*w*, 906*w*, 755*m*, 693*m*. ¹H-NMR: 7.61–7.09 (*m*, 5 arom. H); 3.09–3.66 (*m*, 2 CH₂O); 3.50 (*s*, MeN); 1.92–1.74 (*m*, CH₂(7), CH₂(8)). ¹³C-NMR: 165.7 (*s*, C(2)); 142.1 (*s*, 1 arom. C); 129.2, 123.5, 116.9 (3*d*, 5 arom. CH); 74.6, 67.7 (2*t*, 2 CH₂O); *ca.* 46 (broad, C(3)); *ca.* 37 (broad, C(7)); *ca.* 34 (broad, MeN); 32.3 (*t*, C(8)). The signals for C(2), C(3), C(7), and Me could be detected only after 6.5 h measurement. CI-MS (NH₃): 218 (16), 217 (100, [M + H]⁺). Anal. Calcd for C₁₃H₁₆N₂O: C, 72.19 ; H, 7.46 ; N, 12.95. Found: C, 72.14 ; H, 7.35 ; N, 13.08.

Reaction of *N*-methyl-*N*-phenyl-5-oxa-1-azaspiro[2.5]oct-1-en-2-amine (**6a**) with thiobenzoic acid.

N-{3-[(*N*-Methyl-*N*-phenylamino)thioxomethyl]tetrahydropyran-3-yl}benzamide (**13**). To a solution of **6a**

(73 mg, 0.338 mmol) in CH₂Cl₂ (5 mL) at 0 °C was added drop-wise a solution of freshly distilled thiobenzoic acid (54 mg, 0.389 mmol). After stirring for 10 min, the reaction was almost complete (DC). The solvent was evaporated after stirring for 13 h at rt, and the crude yellow product was purified by CC (SiO₂, hexane/CH₂Cl₂/AcOEt 2:0.5:1) and recrystallized from AcOEt/hexane yielding 112 mg (93%) of **13** as colorless crystals; mp 136–137 °C. Suitable crystals for the X-Ray crystallography were obtained from AcOEt/hexane by slow evaporation of the solvent. IR (KBr): 3330*m*, 3058*w*, 3028*w*, 2999*w*, 2960*m*, 2942*m*, 2914*w*, 2853*m*, 1664*vs*, 1601*m*, 1590*m*, 1581*m*, 1519*vs*, 1486*vs*, 1462*vs*, 1448*vs*, 1431*s*, 1371*vs*, 1288*s*, 1251*s*, 1227*m*, 1204*w*, 1180*w*, 1173*w*, 1147*m*, 1102*vs*, 1086*vs*, 1073*s*, 1042*s*, 1027*s*, 1000*s*, 984*m*, 932*m*, 922*m*, 901*w*, 867*w*, 847*s*, 800*m*, 780*s*, 733*m*, 721*s*, 709*vs*, 695*s*, 670*m*, 641*w*, 623*m*. ¹H-NMR: 7.48–7.43 (*m*, 3 arom. H); 7.35–7.28 (*m*, 2 arom. H); 7.11–7.09 (*m*, 5 arom. H); 5.94 (br. *s*, NH); 4.27 (*dd*, *J* = 11.4, 3.0, 1 H of CH₂(2)(Thp)); 3.96 (*d*, *J* = 11.4, 1 H of CH₂(2)(Thp)); 3.86 (*dd*, *J* = 11.5, 4.7, 1 H of CH₂(6)(Thp)); 3.69 (*s*, MeN); 3.43 (*dt*, *J* = 11.5, 3.2, 1 H of CH₂(6)(Thp)); 2.96 (*dt*, *J* = 13.4, 5.0, 1 H of CH₂(4)(Thp)); 2.77–2.71 (*m*, 1 H of CH₂(4)(Thp)); 1.55–1.50 (*m*, CH₂(5)(Thp)). ¹³C-NMR: 203.5 (*s*, CS); 165.4 (*s*, CO); 147.4, 133.8 (2*s*, 2 arom. C); 131.4, 129.3, 128.1, 127.5, 126.7, 125.0 (6*d*, 10 arom. CH); 75.1, 68.0 (2*t*, C(2)(Thp), C(6)(Thp)); 64.4 (*s*, C(3)(Thp)); 50.7 (*q*, MeN); 32.8, 22.1 (2*t*, C(4)(Thp), C(5)(Thp)). ESI-MS: 377 (100, [M + Na]⁺), 361 (25). Anal. Calcd for C₂₀H₂₂N₂O₂S: C, 67.77; H, 6.26; N, 7.90; S, 9.05. Found: C, 67.83; H, 6.32; N, 7.85; S, 9.28.

Reaction of *N*-methyl-*N*-phenyl-5-oxa-1-azaspiro[2.5]oct-1-en-2-amine (6a) with *Z*-Phe-OH. *Benzyl N-[(S)-1-Benzyl-2-({(R,S)-3-[(N-methyl-N-phenylamino)oxomethyl]tetrahydropyran-3-yl}amino)-2-oxoethyl]carbamate (14)*. To a solution of **6a** (200 mg, 0.925 mmol) in MeCN (2 mL) at 0 °C, a solution of *Z*-Phe-OH (304 mg, 1.018 mmol) in MeCN (1.5 mL) was added. After stirring for 60 h at rt, the solvent was evaporated. Chromatographic purification (CC, SiO₂, hexane/CH₂Cl₂/AcOEt 1:0.5:1) of the residue yielded 476 mg (99%) of dipeptid **14** as a ca. 1:1 mixture of diastereoisomers. Colorless solid; mp 80–82 °C. IR (KBr): 3299*s*, 3061*m*, 3031*m*, 2955*m*, 2854*m*, 1678*vs*, 1639*vs*, 1593*vs*, 1494*vs*, 1453*vs*, 1372*s*, 1237*vs*, 1152*m*, 1089*vs*, 1041*s*, 1028*s*, 1002*w*, 934*w*, 909*w*, 868*w*, 847*w*, 773*m*, 738*s*, 699*vs*, 680*m*. ¹H-NMR (diastereoisomers): 7.42–7.18 (*m*, 13 arom. H); 7.07–7.04 (*m*, 2 arom. H); 5.92, 5.29 (2*s*, NH); 5.26–5.23 (*m*, NH); 5.13–5.00 (*m*, PhCH₂O); 4.15–4.02 (*m*, CH(α)(Phe), 1 H of CH₂(2)(Thp)); 3.64–3.53 (*m*, 1 H of CH₂(2)(Thp), 1 H of CH₂(6)(Thp)); 3.28–3.19 (*m*, 1 H of CH₂(6)(Thp)); 3.16, 3.15 (2*s*, MeN); 3.09–2.86 (*m*, CH₂(Phe)); 2.27–2.02 (*m*, CH₂(4)(Thp)); 1.27–1.07 (*m*, CH₂(5)(Thp)). ¹³C-NMR (diastereoisomers): 169.8, 169.5 (2*s*, 2 CO); 155.8 (*s*, CO(carbamate)); 144.1, 136.4, 136.3, 136.1 (4*s*, 3 arom. C); 129.4, 129.2, 128.5, 128.4, 128.1, 128.0, 127.9, 127.7, 127.2, 127.1, 126.8 (11*d*, 15 arom. CH); 71.6, 71.1 (2*t*, C(2)(Thp)); 67.8, 67.5, 66.8 (3*t*, PhCH₂O, C(6)(Thp)); 59.4, 59.1 (2*s*, C(3)(Thp)); 55.5 (*d*, C(α)H(Phe)); 40.7 (*q*, MeN); 37.8, 37.5 (2*t*, CH₂(Phe)); 29.6, 29.1, 20.9, 20.8 (4*t*,

C(4)(Thp), C(5)(Thp)). ESI-MS: 538 (100, $[M + Na]^+$). Anal. Calcd for $C_{30}H_{33}N_3O_5$: C, 69.88; H, 6.45; N, 8.15. Found: C, 69.58; H, 6.40; N, 8.02.

As it was not possible to separate the diastereoisomers by means of CC, HPLC separation was undertaken. For analytical HPLC, a good separation was achieved with $CH_2Cl_2/MeOH$ 150:1 ($t_{R1} = 62.9$ min, $t_{R2} = 85.6$ min), whereas for preparative HPLC $CH_2Cl_2/MeOH$ 100:1 ($t_{R1} = 44.9$ min, $t_{R2} = 55.7$ min) was appropriate.

Data of the faster eluting diastereoisomer (14'): $t_R = 44.9$ min. 1H -NMR: 7.38–7.12 (*m*, 13 arom. H); 7.10–7.02 (*m*, 2 arom. H); 5.65 (br. *s*, NH); 5.13–5.03 (*m*, $PhCH_2O$, NH); 4.13 (*d*, $J = 12.3$, 1 H of $CH_2(2)(Thp)$); 4.00 (br. *s*, $CH(\alpha)(Phe)$); 3.65–3.61 (*m*, 1 H of $CH_2(2)(Thp)$, 1 H of $CH_2(6)(Thp)$); 3.26 (*t*, $J = 3.7$, 1 H of $CH_2(6)(Thp)$); 3.16 (*s*, MeN); 3.08–2.91 (*m*, $CH_2(Phe)$); 2.16–2.04 (*m*, $CH_2(4)(Thp)$); 1.28–1.23 (*m*, $CH_2(5)(Thp)$). ^{13}C -NMR: 169.9, 169.6 (2*s*, 2 CO); 155.7 (*s*, CO(carbamate)); 144.2, 136.4, 136.2 (3*s*, 3 arom. C); 129.5, 129.4, 128.6, 128.5, 128.3, 128.0, 127.8, 127.2, 127.0 (9*d*, 15 arom. CH); 71.2 (*t*, C(2)(Thp)); 67.7, 67.1 (2*t*, $PhCH_2O$, $CH_2(6)(Thp)$); 59.3 (*s*, C(3)(Thp)); 55.7 (*d*, C(α)H(Phe)); 40.9 (*q*, MeN); 37.7 (*t*, $CH_2(Phe)$); 30.1, 21.0 (2*t*, C(4)(Thp), C(5)(Thp)).

Data of the slower eluting diastereoisomer (14''): $t_R = 55.7$ min. 1H -NMR: 7.32–7.16 (*m*, 13 arom. H); 7.08–7.02 (*m*, 2 arom. H); 5.85 (br. *s*, NH); 5.15–5.01 (*m*, $PhCH_2O$, NH); 4.03 (*d*-like, C(α)H(Phe), 1 H of $CH_2(2)(Thp)$); 3.65 (*d*-like (1 H of $CH_2(6)(Thp)$); 3.55 (*d*, $^2J = 11.4$, 1 H of $CH_2(2)(Thp)$); 3.30–3.21 (*m*, 1 H of $CH_2(6)(Thp)$); 3.17 (*s*, MeN); 3.09–3.02, 2.94–2.88 (2*m*, $CH_2(Phe)$); 2.28–2.04 (*m*, $CH_2(4)(Thp)$); 1.35–1.17 (*m*, $CH_2(5)(Thp)$). ^{13}C -NMR: 169.7 (*s*, 2 CO); 155.9 (*s*, CO(carbamate)); 144.2, 136.4, 136.2 (3*s*, 3 arom. C); 129.4, 128.6, 128.5, 128.2, 128.0, 127.8, 127.4, 127.0 (8*d*, 15 arom. CH); 71.9 (*t*, C(2)(Thp)); 67.9, 67.0 (2*t*, $PhCH_2O$, $CH_2(6)(Thp)$); 59.6 (*s*, C(3)(Thp)); 55.6 (*d*, C(α)H(Phe)); 41.0 (*q*, MeN); 38.0 (*t*, $CH_2(Phe)$); 29.2, 21.1 (2*t*, C(4)(Thp), C(5)(Thp)).

Deprotection of dipeptide (14). *Selective deprotection of the amino group:* N-[3-(*R,S*)-[(*N*-Methyl-*N*-phenylamino)carbonyl]tetrahydropyran-3-yl]-2-(*S*)-amino-3-phenylpropanamide (15). To a solution of 14 (100 mg, 0.194 mmol) in MeOH (4 mL) was added Pd (10%)/C and the suspension was stirred in a H_2 atmosphere for 3 h at rt. Then, the mixture was filtered through *Celite* and the solvent evaporated. The product consisted of two diastereoisomers in a ratio of ca. 1:1. Colorless solid; mp 119–121 °C. IR (KBr): 3398*m*, 3337*s*, 3058*w*, 2946*m*, 2916*m*, 2846*m*, 1669*vs*, 1638*vs*, 1593*s*, 1493*vs*, 1450*s*, 1370*s*, 1314*m*, 1291*m*, 1275*m*, 1233*w*, 1204*m*, 1177*w*, 1149*w*, 1091*vs*, 1026*m*, 920*w*, 864*w*, 845*w*, 785*m*, 758*m*, 715*m*, 704*s*, 667*w*. ESI-MS: 538 (5), 448 (5), 418 (14), 404 (100, $[M+Na]^+$), 289 (3), 275 (15, $[M-C_7H_8N]^+$).

The two diastereoisomers of the product (15) were separated by CC (SiO_2 , $CH_2Cl_2/MeOH = 15:1$).

Data of the faster eluting diastereoisomer (15'): Yield: 20 mg (27%). DC: R_f (CH₂Cl₂/MeOH 15:1) = 0.61. ¹H-NMR: 7.43–7.05 (*m*, 10 arom. H, NH); 4.13 (*dd*, $J = 11.5, 2.4$, 1 H of CH₂(2)(Thp)); 3.83 (*d*, $J = 11.4$, 1 H of CH₂(2)(Thp)); 3.70–3.60 (*m*, 1 H of CH₂(6)(Thp)); 3.40–3.31 (*m*, 1 H of CH₂(6)(Thp)); 3.24 (*s*, MeN); 3.20–3.15 (*m*, 1 H of CH₂(Phe), C(α)H(Phe)); 2.53–2.44 (*m*, 1 H of CH₂(Phe), 1 H of CH₂(4)(Thp)); 2.36–2.26 (*m*, 1 H of CH₂(4)(Thp)); 1.42–1.39 (*m*, CH₂(5)(Thp)). ¹³C-NMR: 172.7, 170.0 (2*s*, 2 CO); 145.0, 137.7 (2*s*, 2 arom. C); 129.1, 128.6, 127.3, 127.0, 126.7 (5*d*, 10 arom. CH); 72.8, 68.0 (2*t*, C(2)(Thp), C(6)(Thp)); 59.1 (*s*, C(3)(Thp)); 56.5 (*d*, C(α)H(Phe)); 41.1 (*q*, MeN); 40.0 (*t*, CH₂(Phe)); 28.2, 21.2 (2*t*, C(4)(Thp), C(5)(Thp)). Anal. Calcd for C₂₂H₂₇N₃O₃ · 1/3 H₂O: C, 69.21; H, 7.20; N, 10.85. Found: C, 69.34; H, 6.97; N, 10.31.

Data of the slower eluting diastereoisomer (15''): Yield: 21 mg (28%). DC: R_f (CH₂Cl₂/MeOH 15:1) = 0.47. ¹H-NMR: 7.38–7.16 (*m*, 10 arom. H, NH); 4.36 (*dd*, $J = 11.6, 2.3$, 1 H of CH₂(2)(Thp)); 3.86–3.79 (*m*, 1 H of CH₂(2)(Thp), 1 H of CH₂(6)(Thp)); 3.43–3.25 (*m*, 1 H of CH₂(6)(Thp), C(α)H(Phe), 1 H of CH₂(Phe)); 3.23 (*s*, MeN); 2.47 (*dd*-artig, 1 H of CH₂(Phe)); 2.31–2.12 (*m*, CH₂(4)(Thp)); 1.62–1.44 (*m*, CH₂(5)(Thp)). ¹³C-NMR: 172.6, 170.8 (2*s*, 2 CO); 145.0, 138.2 (2*s*, 2 arom. C); 129.1, 129.1, 128.5, 127.3, 127.1, 126.6 (6*d*, 10 arom. CH); 70.9, 67.6 (2*t*, C(2)(Thp), C(6)(Thp)); 58.2 (*s*, C(3)(Thp)); 56.6 (*d*, C(α)H(Phe)); 40.9 (*q*, MeN); 40.1 (*t*, CH₂(Phe)); 30.9, 21.2 (2*t*, C(4)(Thp), C(5)(Thp)).

Selective deprotection of the carboxyl group: 3-({2-[(Benzyloxycarbonyl)amino]-3-phenylpropanoyl}-amino)tetrahydropyran-3-carboxylic acid (**16**). To a solution of **14** (200 mg, 0.388 mmol) in THF (3 mL) at 0 °C was added 6N HCl in H₂O/THF 1:1 (3 mL), and the mixture was stirred at rt for 4 h. Then, the solvent was evaporated, and CC of the residue (SiO₂, CH₂Cl₂/MeOH/AcOH 100:4:1) yielded 50 mg (25%) of starting **14** and 96 mg (58%, 78% with regard to consumed **14**) **16** as colorless crystals (1:1 mixture of diastereoisomers (¹H-NMR)); mp 76–79 °C. IR (KBr): 3306*s*, 3063*s*, 3031*s*, 2956*s*, 2859*s*, 2632*w*, 1715*vs*, 1670*vs*, 1582*m*, 1530*vs*, 1498*vs*, 1466*s*, 1454*s*, 1384*m*, 1289*s*, 1245*vs*, 1202*s*, 1152*m*, 1091*vs*, 1055*s*, 1039*s*, 1003*w*, 937*w*, 906*w*, 869*w*, 846*m*, 773*w*, 744*s*, 698*vs*, 646*w*, 608*w*. ¹H-NMR (diastereoisomers): 10.72 (broad *s*, COOH); 7.34–6.92 (*m*, 10 arom. CH, NH); 5.98, 5.88 (2*d*, $J = 7.2, 7.1$, NH(Phe)); 5.04, 5.03 (2*s*, PhCH₂O); 4.60–4.53 (*m*, C(α)H(Phe)); 3.91–3.73 (*m*, CH₂(2)(Thp)); 3.66–3.51, 3.38–3.26 (2*m*, CH₂(6)(Thp)); 3.14–2.97 (*m*, CH₂(Phe)); 2.27–2.20, 2.00–1.88 (2*m*, CH₂(4)(Thp)); 1.44–1.31 (*m*, CH₂(5)(Thp)). ¹³C-NMR (diastereoisomers): 176.1, 173.9, 173.8 (3*s*, 2 CO); 156.2 (*s*, CO(carbamate)); 136.3, 136.2, 136.0 (3*s*, 2 arom. C); 129.4, 129.3, 128.5, 128.4, 128.3, 127.9, 127.8, 126.8 (8*d*, 10 arom. H); 71.3, 71.2 (2*t*, C(2)(Thp)); 68.0 (*t*, PhCH₂O); 66.9 (*t*, C(6)(Thp)); 57.9, 57.8 (2*s*, C(3)(Thp)); 38.2, 38.0 (2*t*, CH₂(Phe)); 28.0, 27.6 (2*t*, C(4)(Thp)); 20.9, 20.7 (2*t*, C(5)(Thp)). CI-MS (NH₃): 444 (8, [M+NH₄]⁺), 427 (10, [M+H]⁺), 409 (100, [M–OH]⁺), 398 (7), 220 (8), 108 (26).

The separation of the diastereoisomers by means of CC was not possible.

*X-Ray Crystal-Structure Determination of 13 (Figure 1).*⁴² All measurements were made on a Nonius KappaCCD area-detector diffractometer⁴³ using graphite-monochromated MoK α radiation ($\lambda = 0.71073$ Å) and an Oxford Cryosystems Cryostream 700 cooler. Data collection and refinement parameters are given below, and a view of the molecule is shown in *Figure 1*. Data reduction was performed with HKL Denzo and Scalepack.⁴⁴ The intensities were corrected for Lorentz and polarization effects, and an absorption correction based on the multi-scan method⁴⁵ was applied. Equivalent reflections were merged. The structure was solved by direct methods using SIR92,⁴⁶ which revealed the positions of all non-hydrogen atoms. The non-hydrogen atoms were refined anisotropically. The amide H-atom was placed in the position indicated by a difference electron density map and its position was allowed to refine together with an isotropic displacement parameter. All remaining H-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent atom ($1.5U_{eq}$ for the methyl group). The refinement of the structure was carried out on F^2 by using full-matrix least-squares procedures, which minimized the function $\sum w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied. Neutral atom scattering factors for non-H-atoms were taken from ref.⁴⁷, and the scattering factors for H-atoms were taken from ref.⁴⁸ Anomalous dispersion effects were included in F_c ,⁴⁹ the values for f' and f'' were those of ref.⁵⁰ The values of the mass attenuation coefficients are those of ref.⁵¹ All calculations were performed using the SHELXL97 program.⁵² Crystal data for **13**: Crystallized from AcOEt/hexane, C₂₀H₂₂N₂O₂S, $M = 354.47$, colorless, prism, crystal dimensions $0.13 \times 0.15 \times 0.25$ mm, monoclinic, space group $P2_1/n$, $Z = 4$, reflections for cell determination 40559, 2θ range for cell determination $4-60^\circ$, $a = 7.6476(1)$ Å, $b = 18.0707(3)$ Å, $c = 13.3764(2)$ Å, $\beta = 105.9588(7)^\circ$, $V = 1777.34(5)$ Å³, $D_X = 1.325$ g·cm⁻³, $\mu(\text{MoK}\alpha) = 0.198$ mm⁻¹, $T = 160(1)$ K, ϕ and ω scans, $2\theta_{\text{max}} = 60^\circ$, transmission factors (min; max) 0.770; 0.977, total reflections measured 51740, symmetry independent reflections 5194, reflections with $I > 2\sigma(I)$ 3611, reflections used in refinement 5194, parameters refined 232, final R (on F ; $I > 2\sigma(I)$ reflections) = 0.0507, wR (all data) = 0.1397 ($w = [\sigma^2(F_o^2) + (0.0638P)^2 + 0.5508P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$, goodness of fit 1.051, secondary extinction coefficient 0.016(2), final $\Delta_{\text{max}}/\sigma = 0.001$, $\Delta\rho$ (max; min) = 0.71; -0.33 e Å⁻³.

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